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(54) Multiphase Combination Preparation and Its Use for Oral Contraception

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Abstract

A ~~multistage~~ *multiphase* combination preparation is useful for oral contraception and comprises a surprisingly low amount of gestodene as the gestagen and comprises ethinylestradiol as the estrogen.

This invention relates to a multiphase combination preparation made up of 21 or 28 units, each to be administered on separate days, and its use for oral contraception for females of child bearing age.

Multiphase combination preparations for oral contraception are known, for example, from DE-A 2,365,103 (USP 3,957,982) and the patents derived therefrom. Usually two or three stages are involved. These multiphase preparations consist of 21 or 28 dragees, and contain, in the first stage, 4-6 dragees wherein each dragee contains an amount of estrogen corresponding to 0.02-0.05 mg of ethinylestradiol, and an amount of gestagen (progestogen) corresponding to 0.04-0.09 mg of d-norgestrel; in the second stage, (which can be a continuation of the first in essence), 4-6 dragees each containing onefold to twofold the amount of estrogen of the first stage, for example 0.03-0.05 mg of ethinylestradiol, and onefold to one and one-half-fold the amount of gestagen of the first stage, for example 0.05-0.125 mg of d-norgestrel; and, in the third stage, 9-11 dragees each containing an amount of estrogen that is larger than or exactly as large as that in the first stage and smaller than or exactly as large as in that in the second stage, for example, 0.025-0.050 mg of ethinylestradiol, and an amount of gestagen larger than that in the second stage, but no larger than three times as large as that in the first stage, for example 0.10-0.25 mg of d-norgestrel, and optionally, in the fourth stage, 7 dragees without estrogen and without gestagen. The number of dosage units in the three stages which contain estrogen and gestagen amounts to 21; to adapt to the 28-day cycle, 7 units free of active ingredient can be additionally included with the 21 units containing active agent.

Such multiphase preparations provide higher compatibility and improved cycle control as compared with the known combination preparations for cyclic or sequential usage.

European Patent Application No. 81200240 (publication number 36229) describes a varient of a multiphase preparation. This version is characterized in that the units of the first stage contain a higher amount of estrogen than the units of the subsequent stage.

In the multiphase combination preparations, the estrogens can be utilized in amounts smaller than 0.05 mg of ethinylestradiol. Because of their staggered structures, the amounts of gestagen can likewise be kept at a low level. In this way, contraceptives are obtained using the lowest amounts of hormones thus practiced.

However, it is still desirable that the amount of gestagen be lowered still further.

The invention provides a new combination for oral contraception utilizing significantly lower amounts of gestagens.

It has now been found that the amount of gestagen in multiphase combination preparations can be still further reduced by utilizing, as the gestagen, gestodene (17α-ethinyl-17β-hydroxy-18-methylestra-4,15-dien-3-one). Entirely unexpectedly, in spite of reduction of the gestagen does, an excellent cycle control with good compatibility is attained. Contraceptive safety is ensured in all instances.

Accordingly, the present invention provides a multiphase combination preparation for oral contraception made up of 21 and/or 28 units of administration of one unit per day, wherein, in a first phase of 4-6 units, each unit contains an estrogen in a low dose and a gestagen in a low dose and, in a second phase of 4-6 units, each unit contains an estrogen with the same dose or a slightly raised dose, at most increased to twofold, and a gestagen with the same or a slightly raised dose, maximally increased to one and one-half-fold and, in a third

stage of 9-11 units, each unit contains an estrogen with the same dose or a dose lowered again, maximally to the initial value, and a gestagen with a further raised dose, maximally to three times the initial value, and the three phases together consist of 21 units, optionally followed by seven further units without estrogen and without gestagen, characterized in that the gestagen is gestodene and the estrogen is ethinylestradiol, and the amount of ethinylestradiol in the first phase does not exceed 0.05 mg and of gestodene in the first phase does not exceed 0.07 mg.

The invention furthermore relates to the use of the multiphase combination preparation for oral contraception. One unit of administration is given daily in the indicated stage sequence. The total number of days on which administration of the active agent combination takes place is to be in all cases 21, followed by 7 hormone-free days on which there are administered daily either 1 placebo or no units of administration.

Per this invention, the amount of gestagen can be lowered to values which are less than those equivalent to the lowest amount permitted in U.S. 3,957,982, i.e., amounts equivalent to 0.04 mg of d-norgestrel.

The units of administration preferably contain, in the initial 4-6 days, 0.02-0.05 mg of ethinylestradiol and 0.04-0.07 mg of gestodene per unit. The amount of ethinylestradiol utilized according to this invention in the 4-6 days of the second phase preferably is per unit, 0.03-0.05 mg, and the amount of gestodene per unit is preferably 0.05-0.10 mg. The amount of ethinylestradiol utilized according to the invention in the 9-11 days of the third phase, per unit, is preferably 0.02-0.05 mg and the amount of gestodene per unit is preferably 0.08-0.12 mg.

Ethinylestradiol and gestodene are preferably administered orally in combination; however, they can also be administered separately and/or parenterally as a contemplated equiva-

lent. Thus, the term "unit" herein contemplates both a single composition with the estrogens and gestagens admixed and also two separate compositions in a single unit, each one having one of the gestagen and the estrogen.

Ethinylestradiol and gestodene are processed, together with the additives, excipients and/or flavoring agents customary in galenic pharmacy, in accordance with the conventional methods into the usual forms of administration. For preferred oral administration, suitable are, in particular, tablets, dragees, capsules, pills, suspensions, or solutions. Such details are well known, see, e.g., USP 3,957,982.

The 21 units of administration which contain active agent can be supplemented by 7 units of administration free of active agent (placebos) in order to bridge the days on which no hormones are to be administered. In this way, the habit of taking one unit per day is maintained. It is then merely necessary to continue, after 28 days (after withdrawal bleeding), with a new package of tablets.

The active agents can also be incorporated into film material as contemplated equivalents. By conventionally subdividing the film layer, units of administration can be made available with a corresponding dosage for buccal or sublingual administration. See Example 1.

Accordingly, the invention also concerns pharmaceutical, packaged items (birth control kits) characterized by containing multiphase combination preparations in 21 or 28 units of administration in a matched, fixedly determined sequence, the sequence corresponding to the phases of daily administration. The placebos and the units of administration of the three stages suitably differ in their color or shape.

The pharmaceutical package can be designed, inter alia,

in the form of a see-through pack with, for example, 6 dragees of the first phase, 5 dragees of the second phase, 10 dragees of the third phase, and optionally 7 placebos, each of which is respectively removable daily, i.e. over 21 or 28 days.

In general, the birth control combination and method of this invention are made and used conventionally, except as noted otherwise herein,e.g., analogously to the product.

The combination preparation of the invention is discussed primarily in terms of a three-phase regimen; however, all combinations and method literally within the description are included, e.g., two phase versions wherein the amounts of gestagen and estrogen in "phases" one and two above are the same.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. In the following examples, all temperatures are set forth uncorrected in degrees Celsius; unless otherwise indicated, all parts and percentages are by weight.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

Example 1 (Dragee Composition)

First phase	0.030 mg	Ethinylestradiol
(6 dragees)	0.050 mg	Gestodene
	37.455 mg	Lactose
	15.500 mg	Corn starch
	0.065 mg	Calcium disodium edetate
	1.700 mg	"Kollidon" 25 (a trademark)

0.200 mg		Magnesium stearate
55.000 mg		Total weight, supplemented to 90.000 mg with the usual sugar mixture and optionally coloring.
Second phase (5 dragees)	0.040 mg	Ethinylestradiol
	0.070 mg	Gestodene
	37.425 mg	Lactose
	15.500 mg	Corn starch
	0.065 mg	Calcium disodium edetate
	1.700 mg	"Kollidon" 25 (a trademark)
	0.200 mg	Magnesium stearate
	55.000 mg	Total weight, supplemented to 90.00 mg with the usual sugar mixture and optionally coloring.
Third phase (10 dragees)	0.030 mg	Ethinylestradiol
	0.100 mg	Gestodene
	37.405 mg	Lactose
	15.500 mg	Corn starch
	0.065 mg	Calcium disodium edetate
	1.700 mg	"Kollidon" 25 (a trademark)
	0.200 mg	Magnesium stearate
	55.000 mg	Total weight, supplemented to 90.000 mg with the usual sugar mixture and optionally coloring.

Clinical Investigations on Compatibility and Contraceptive Safety

The three-phase preparation according to Example 1 of the present invention (A) was compared with the three-phase

preparation according to the example in German Published Application 2,365,103 (USP 3,957,982)(B).

Test preparation A was used for treating 377 women of childbearing age in 2,123 cycles, and test preparation B was used to treat 362 women of childbearing age in 2,088 cycles. Each of the women received daily one dragee for 21 days; the subsequent 7 days, during which withdrawal bleeding took place, were left without administering anything. This form of administration was retained over 6 cycles. Most of the women participated in the trial until the end.

No pregnancies occurred during the entire treatment period.

Both preparations were well compatible.

In case of three-phase preparation A, less intracyclic menstrual bleeding occurred than in case of three-stage preparation B.

Cycle		1st	3rd	6th
Spotting	A	11.8	7.4	3.1
	B	15.9	11.9	5.9
Withdrawal Bleeding	A	2.0	1.5	0.9
	B	0.9	0.9	0.9
Spotting and Withdrawal Bleeding	A	1.1	0.9	0.3
	B	2.9	1.8	1.2

The good cycle control in the case of A is surprising since A has a lower dosage of the gestagen proportion than B.

The preceding examples can be repeated with similar success by substituting the generically or specifically described

reactants and/or operating conditions of this invention for those used in the preceding Examples.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A multiphase combination composition suitable for oral contraception comprising 21 separate dosage units suitable for daily administration of one dosage unit per day consisting essentially of as a first phase 4-6 units comprising, in admixture with a pharmaceutically acceptable carrier, ethinylestradiol as estrogen in a low contraceptively effective dose of up to 0.05 mg and gestodene as gestagen in low contraceptively effective dose of up to 0.07 mg; as a second phase, 4-6 units comprising, in admixture with a pharmaceutically acceptable carrier, ethinylestradiol in the same dose or a higher dose than that of the first phase, up to twice the first-phase dose, and gestodene in the same or a higher dose than that of the first phase up to one and one-half that of the first-phase and, as a third phase, 9-11 units comprising, in admixture with a pharmaceutically acceptable carrier, ethinylestradiol in the same dose or a lower dose than the second phase, as low as that of the first phase, and gestodene in a dose higher than that of the second phase, up to three times that of the first phase.

2. A composition of claim 1, further comprising, as a fourth stage, 7 separate placebo dosage units containing no estrogen and no gestagen.

3. A compound of claim 1, wherein the dosage units of administration in the first stage contain 0.02-0.05 mg of ethinylestradiol and 0.04-0.07 mg of gestodene; in the second stage contain 0.03-0.05 mg of ethinylestradiol and 0.05-0.10 mg of gestodene; and in the third stage contain 0.02-0.05 mg of ethinylestradiol and 0.08-0.12 mg of gestodene.

5. A composition of claim 1, wherein the number of dosage units in the first stage is 6, in the second stage 5, and

In the third stage 10.

6. A composition of claim 1, wherein the dosage units are tablets or dragees.

7. A composition of claim 1, wherein the first stage consists essentially of 6 dragees, each dragee containing about 0.03 mg of ethinylestradiol and about 0.05 mg of gestodene, the second stage consists essentially of 5 dragees, each dragee containing about 0.04 mg of ethinylestradiol and about 0.07 mg of gestodene, and the third stage consists essentially of 10 dragees, each dragee containing about 0.03 mg of ethinylestradiol and about 0.10 mg of gestodene.

8. A composition of claim 1, wherein the estrogen and the gestagen are mixed together in each dosage unit.

9. A composition of claim 1, wherein the dosage units are film layers.

10. A composition of claim 1, in the form of a kit comprising the 21 dosage units in a single package from which each is separately and independently removable.

11. A composition of claim 2, in the form of a kit comprising the 28 dosage units in a single package from which each is separately and independently removable.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente